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Serial Head and Brain Imaging of 17 Fetuses With Confirmed Zika Virus Infection in Colombia, South America

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Abstract

Objective—To evaluate fetal ultrasound and magnetic resonance imaging findings among a series of pregnant women with confirmed Zika virus infection to evaluate the signs of congenital Zika syndrome with respect to timing of infection.

Methods—Retrospective case series of pregnant women referred to two perinatal clinics in Barranquilla and Ibagué, Colombia with findings consistent with congenital Zika syndrome and Zika virus infection confirmed in maternal, fetal, or infant samples. Serial ultrasound measurements, fetal magnetic resonance imaging results, laboratory results, and perinatal outcomes were evaluated.

Results—We describe 17 cases of confirmed prenatal maternal Zika virus infection with adverse fetal outcomes. Among the 14 symptomatic women, the median gestational age for maternal Zika virus symptoms was 10 weeks (range 7–14). The median time between Zika virus symptom onset and microcephaly (head circumference less than 3 standard deviations below the mean) was 18 weeks (range 15–24). The earliest fetal head circumference measurement consistent with microcephaly diagnosis was at 24 weeks of gestation. The earliest sign of congenital Zika

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syndrome was talipes equinovarus, which in two patients was noted first at 19 weeks. Common findings on fetal magnetic resonance imaging were microcephaly, ventriculomegaly, polymicrogyria, and calcifications.

Conclusion—Our analysis suggests a period of at least 15 weeks between maternal Zika virus infection in pregnancy and development of microcephaly, and highlights the importance of serial and detailed neuroimaging.

Introduction

Zika virus is primarily transmitted through the bite of an infected *Aedes* species mosquito, however it can also be spread via sexual transmission (1, 2) and vertically--from an infected pregnant woman (3, 4).

The Colombian *Instituto Nacional de Salud* (INS, National Health Institute) began official surveillance for symptomatic Zika virus disease in August 2015 (5). By November 26, 2016, there were 19,448 pregnant women with symptomatic Zika virus disease reported to INS; most were not tested but 5,882 had laboratory-confirmed Zika virus infection.

Although the natural history of congenital Zika virus infection is still under active investigation, the virus is an infectious teratogen that can cause significant neurologic sequelae and birth defects in infants infected through maternal-fetal transmission (6, 7). Congenital Zika virus infection is associated with fetal brain abnormalities including microcephaly (7, 8). Previous reports have shown that these abnormalities, including microcephaly, ventriculomegaly, abnormalities of the corpus callosum, cortical migration abnormalities and intracranial calcifications, can be detected by prenatal ultrasound (9–11). In order to identify abnormalities and monitor growth of fetuses whose mothers have laboratory evidence of Zika virus infection, the U.S. Centers for Disease Control and Prevention and INS recommended that for these women ultrasounds every 3–4 weeks should be considered(12–14)

The purpose of this report is to demonstrate the timing of ultrasound findings consistent with congenital Zika syndrome after laboratory confirmed maternal Zika virus infection.

Materials and Methods

Between December 2015 and September 2016 two private perinatal referral clinics in Barranquilla and Ibagué, Colombia, provided care to pregnant women with laboratory-confirmed or suspected Zika virus infection. Women were included in this series if Zika virus RNA was detected by reverse transcription polymerase chain reaction in either a maternal serum or urine sample, amniotic fluid, placenta, cord or infant serum sample, and if findings consistent with congenital Zika syndrome (6) were present on fetal ultrasound or magnetic resonance imaging (15, 16). These women were selected to focus on the measurement of fetal head circumference and other ultrasound parameters in pregnancies affected by congenital Zika syndrome. Medical records were abstracted by multiple staff members in each clinic to ascertain demographic characteristics such as maternal age and obesity (defined as body mass index ≥30 kg/m^2), presence and timing of maternal or

paternal Zika virus symptoms, maternal and infant laboratory results, prenatal ultrasound and magnetic resonance imaging results, and perinatal outcomes. Maternal and infant Zika virus testing was performed at the central Public Health Laboratory in Bogotá (5) using reverse transcription polymerase chain reaction methods that have been previously described (17).

Ultrasound examinations were performed using Voluson E8 Ultrasound (GE Healthcare Ultrasound, Milwaukee, WI, USA). All images were reviewed to assess fetal brain anatomy and growth by at least two maternal fetal medicine specialists who were aware of the women's Zika virus infection status. The first trimester was defined as <14 weeks of gestation. For the ultrasound measurements microcephaly was defined as head circumference more than 3 standard deviations below the mean for gestational age; for the postnatal measurements the 3rd percentile for gestational age and sex was used, according to Intergrowth 21st fetal growth standards (18). Fetal magnetic resonance imaging was performed to better assess cortical development using a Philips Achieva 1.5 Tesla magnetic resonance imaging system (Philips North America, Andover, MA, USA).

We describe characteristics of the pregnant women and report clinical details about the pregnancy including delivery information. We report the timing and results of ultrasounds and magnetic resonance imaging, and compared ultrasound measurements to the Intergrowth-21st fetal growth standards and postnatal sex-specific head circumference standards (19). This investigation was approved by the institutional review boards governing the two perinatal clinics. Informed consent for serial fetal imaging such as ultrasound and magnetic resonance imaging was obtained from all study participants. Statistical analyses were performed using IBM SPSS Statistics version 23.0. In accordance with United States federal human subjects protection regulations at 45 CFR §46.101c and §46.102d and with the Guidelines for Defining Public Health Research and Public Health Non-Research, the analysis of these data was reviewed by the human subjects protection coordinator at the National Center on Birth Defects and Developmental Disabilities of the CDC and determined to be non-research, exempt from institutional review board evaluation.

Results

We describe 17 cases of maternal prenatal Zika virus infection confirmed by reverse transcription polymerase chain reaction with evidence of congenital Zika syndrome. The median maternal age was 23 years (range 16–31) and the median pre-pregnancy body mass index was 24.0 kg/m^2 (range 17.3–32.8). First trimester dating ultrasound information was available for 13 women (77%). Among the 14 symptomatic women, the median gestational age at onset of Zika virus disease symptoms was 10 weeks (range 7–14) (Appendix 1, available online at http://links.lww.com/xxx). Of the three asymptomatic women, one had a partner with symptoms (fever, arthralgia and rash) around the time of conception. This couple subsequently had sex without using condoms, making sexual transmission likely; amniotic fluid samples taken at 20 weeks of gestation were reverse transcription polymerase chain reaction positive for Zika virus. The other two asymptomatic women were diagnosed with Zika virus infection by the detection of Zika virus RNA in amniotic fluid at 28 and 33 weeks of gestation respectively, after prenatal ultrasound findings were found to be

suggestive of congenital Zika syndrome. For 10 women, all tested samples were positive for Zika virus infection by reverse transcription polymerase chain reaction; the remaining seven women had both positive and negative samples (Appendix 1, http://links.lww.com/xxx).

Most pregnancies had a full evaluation for other etiologies for birth defects to rule out other causes. All women had testing for other congenital infections; none of the tested samples had evidence of toxoplasmosis, syphilis, or herpes. Patient 7 had positive immunoglobulin G and immunoglobulin M for cytomegalovirus in maternal serum, although the amniotic fluid was negative for cytomegalovirus. Of the 15 infants who had chromosomal analysis or karyotyping performed, 14 were normal; patient 7 had a micro-duplication of chromosome 14q32, which was deemed to have no clinical relevance.

The median number of weeks between Zika virus disease symptoms and the first non-dating ultrasound was 8 weeks (range 3–20). For 15 of the 17 infants, microcephaly was observed by prenatal ultrasound imaging. The median gestational age at which the head circumference was noted to be less than 3 standard deviations below the mean was 28 weeks (range 24 – 33). The median time from maternal report of Zika virus disease symptoms to ultrasound observation of microcephaly was 18 weeks (range 15–24). For three patients earlier signs of congenital Zika syndrome were observed before the microcephaly diagnosis: *talipes equinovarus* (club foot) at 19.3 weeks for patient 7 and ventriculomegaly at 21.5 and 22.0 weeks for patients 13 and 3, respectively (Table 1). These defects are part of the congenital Zika syndrome phenotype, and are likely a result of earlier brain damage. Patient 14 never received a microcephaly diagnosis, but this infant had dysgenesis of the cerebellar vermis, which was the only sign of congenital Zika syndrome noted prenatally. Patient 16 had *talipes equinovarus* noted at 19.3 weeks and several brain abnormalities were observed at 21 weeks of gestation.

The serial prenatal ultrasound findings demonstrate fetal head circumference measurements relative to 3 standard deviations below the mean from Intergrowth 21st for the 13 patients with Zika virus symptoms in the first trimester (Appendix 2, available online at http://links.lww.com/xxx). Ultrasounds performed between gestational weeks 20–24 did not show head circumferences below 3 standard deviations below the mean, whereas the next ultrasounds for these patients did. The timing of onset of Zika virus disease symptoms, positive laboratory reverse transcription polymerase chain reaction results, ultrasounds, and observation of a fetal head circumference more than 3 standard deviations below the mean and the end of pregnancy are displayed for all 17 patients in Figure 1.

As part of the study protocol, a fetal magnetic resonance imaging was offered and performed in 16 patients (Table 1). The median gestational age at fetal magnetic resonance imaging was 32.3 weeks (range 21–38). The magnetic resonance imaging confirmed the ultrasound findings and provided additional information including nine cases with involvement of the corpus callosum. In six cases there was evidence of polymicrogyria.

The median gestational age at birth was 38.0 weeks. For 6 of 17 infants the birthweights were below the 10th percentile according to Intergrowth 21st standards (19) . All 5 minute Apgar scores were 9 or 10. At delivery, the occipitofrontal circumference was less than the

3rd percentile for the 15 infants that were prenatally diagnosed with microcephaly. The head circumference for case infant 14, the infant with dysgenesis of the cerebellar vermis, was just above the mean immediately after birth; however, when this child was seen 30 days after birth the head circumference was more than one standard deviation below the mean for age and sex.

Discussion

This case series provides unique information on the trajectory of fetal head circumference after laboratory-confirmed maternal Zika virus infection for infants eventually diagnosed with congenital Zika syndrome; at least 15 weeks elapsed from maternal Zika virus disease symptoms to the detection of fetal microcephaly, with the earliest diagnosis of microcephaly occurring at 24 weeks of gestation.

Talipes equinovarus, the first sign for two patients, has been seen in previously reported Zika cases and might be due to damage to the corticospinal tract or to the central or peripheral motor neurons (20). Other ultrasound findings included arthrogryposis, ventriculomegaly, intracranial calcifications, dysgenesis or agenesis of the corpus callosum, dysgenesis of the cerebellar vermis and reduction in brain volume, which are consistent with a literature review of congenital Zika syndrome (6). Central nervous system anomalies were seen as early as 4 weeks after maternal infection in French Guiana, earlier than the 8 weeks we observed for ventriculomegaly in patient 13, indicating the brain is affected before microcephaly is observed (21).

Limitations of this analysis include the fact that this was a convenience sample of women who sought care with these two clinics and that this was a retrospective analysis of available data for women mostly infected in the first trimester. Other limitations include the potential for error in the self-reported timing of Zika virus symptoms; error in head circumference measurements, especially in early ultrasounds; and the fact that the number and spacing of ultrasounds for all included patients is not consistent due to varying time of referral.

A summary of previous publications with information about the timing of prenatal diagnosis of microcephaly in pregnancies affected by Zika virus infection is consistent with the findings in our analysis (Appendix 3, available online at http://links.lww.com/xxx). Of the 37 fetuses previously reported in the literature, the median gestational age when Zika symptoms (mostly rash) were observed in the pregnant woman was 10 weeks and the median gestational age at microcephaly diagnosis was 32 weeks. The median number of weeks between Zika virus symptoms and microcephaly diagnosis was 21 weeks (range 3–29) in these other reports. It should be noted that not all of the previously reported cases had laboratory confirmed Zika and not all had serial ultrasounds, thus affecting the ability to diagnose microcephaly earlier in pregnancy (3, 9, 11, 22–26). The variety of head circumference standards used, and microcephaly definition (-3 standard deviations versus 3rd percentile) also make comparisons challenging.

This analysis of prenatal ultrasound and fetal magnetic resonance imaging findings among a small case series of pregnancies affected by Zika virus infection can inform maternal-fetal

medicine specialists who are managing pregnant women with Zika virus infection, including the more than 1,700 pregnant women with Zika virus infection who have been reported to the U.S. Zika Pregnancy Registry in the 50 U.S. states as of March 2017 (27). It is important to note that among these 17 pregnancies, fetal microcephaly before the 24th week of gestation was not observed, and no microcephaly was observed before 15 weeks had passed since Zika virus symptoms. This informs understanding of the natural history of perinatal Zika virus infection, and cautions against falsely reassuring patients with a normal ultrasound within a few months from presumed maternal infection. It is important to continue following pregnant women with serial ultrasounds. Continued transmission in subsequent seasons is anticipated; obstetric providers will need to continue to counsel pregnant women about exposure to *Aedes* mosquitos, assess travel history and sexual exposure, and--if indicated--test for Zika virus infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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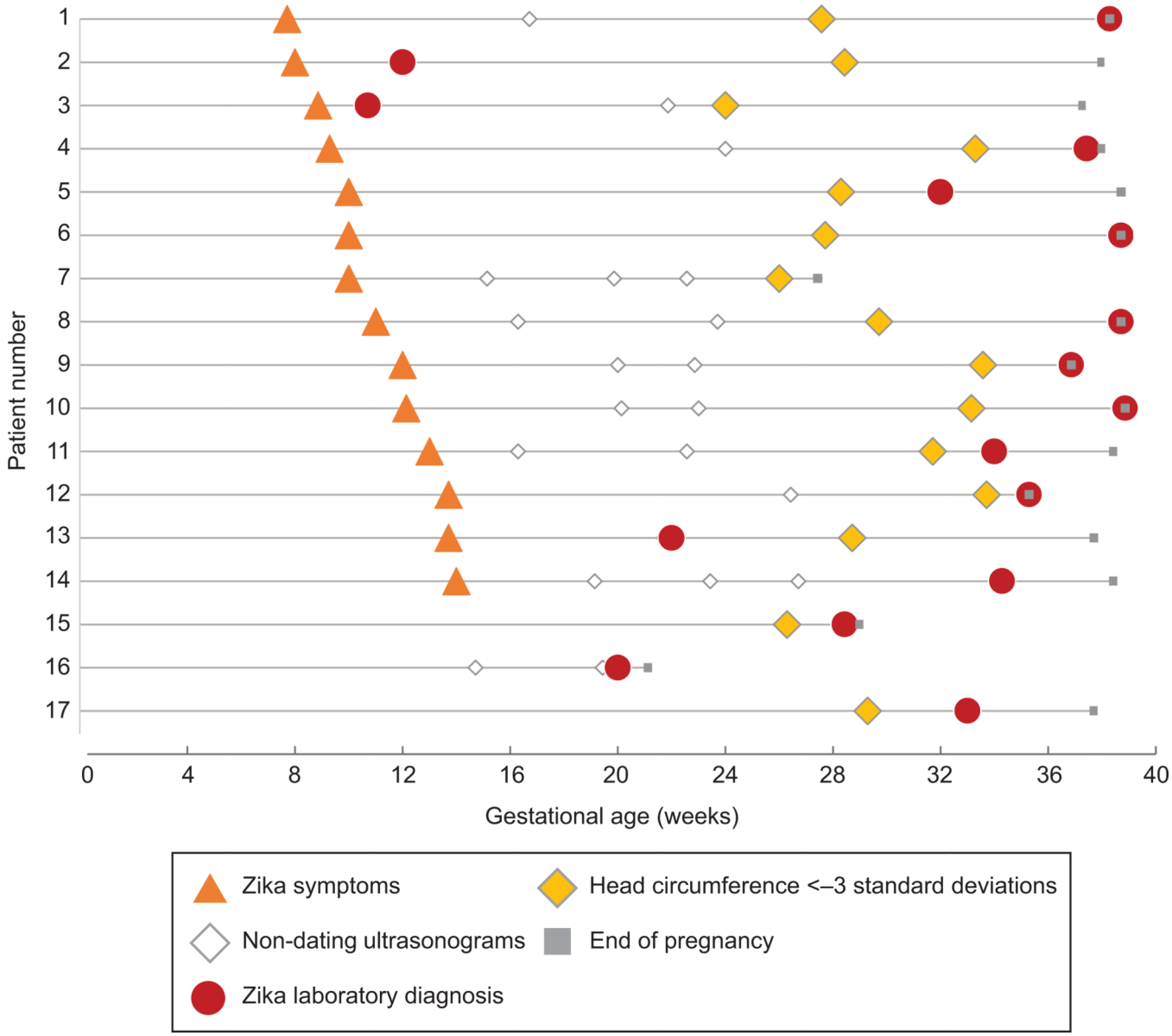

Figure 1.

Timing of maternal Zika virus symptoms, Zika virus laboratory testing, microcephaly diagnosis (ultrasonogram head circumference <–3 standard deviations based on Intergrowth 21*st*), and end of pregnancy for 17 patients. Barranquilla and Ibagué. Colombia, 2015–2016.

Table 1

Ultrasound and magnetic resonance imaging findings for 17 pregnant women with confirmed prenatal Zika virus infection and ultrasound findings consistent with congenital Zika syndrome in the fetus, Barranquilla and Ibagué, Colombia, 2015–2016.

Patient Number	Infant sex	Total number of (non-dating) ultrasounds	First sign of congenital Zika syndrome (weeks gestation)	Timing of ultrasound microcephaly diagnosis (weeks gestation)	Weeks between Zika symptoms and microcephaly diagnosis	Magnetic resonance imaging timing and results								Gestational age (weeks) and weight (grams) at delivery	Head circumference at birth cm (%*)
						(weeks gestation)	Microcephaly	Ventriculomegaly	Polymicrogyria	Reduction in brain volume	Calcifications	Absence/dysgenesis corpus callosum	Cerebellar malf.		
1	Female	3	Microcephaly (27.4)	27.4	19.6	32.3	X		X		X	X		38 / 2810	29.5 (0.13)
2	Female	1	Microcephaly and others (28.3)	28.3	20.3	29.1	X		X			X		38 / 2200	28.0 (0.00)
3	Male	5	Ventriculomegaly (22.0)	24.0	15.1	26.1	X	X				X		37 / 1963	26.0 (0.00)
4	Male	4	Microcephaly (33.2)	33.2	24.0	36.6	X							38 / 3000	29.0 (0.06)
5	Female	1	Microcephaly (28.2)	28.2	18.2	28.0	X		X	X	X			38 / 1800	28.0 (0.00)
6	Female	3	Microcephaly (27.5)	27.5	17.5	N/A								38 / 2810	27.0 (0.00)
7	Female	4	Talipes equinovarus (19.3)	26.0	16	26.2	X		X	X	X			27 / 800	20.4 (0.12)
8	Male	4	Microcephaly (23.5)	29.5	18.5	33.2	X	X			X			38 / 3050	30.5 (0.37)
9	Female	4	Microcephaly (33.4)	33.4	21.4	33.4	X	X			X	X		36 / 2595	29.0 (0.22)
10	male	5	Microcephaly (33.1)	33.1	21.0	33.1	X	X			X	X		38 / 2920	29.1 (0.01)
11	Male	3	Microcephaly (31.5)	31.5	18.5	36.5	X	X		X				38 / 2780	30.0 (0.17)
12	Female	3	Microcephaly (33.4)	33.5	20.0	34.1	X	X	X		X	X		35 / 2410	24.0 (0.00)
13	Male	5	Ventriculomegaly (21.5)	28.5	15.0	28.0	X	X		X		X		37 / 2300	25.0 (0.00)
14	Female	4	Dysgenesis cerebellar vermis (26.5)	N/A†	N/A†	27.3							X	38 / 2530	34.0 (76.05)
15	Female	3	Microcephaly (26.2)	26.2	Asymptomatic	29.0	X	X			X	X		29 / 1000	23.5 (2.61)
16	Male	3	Talipes equinovarus (19.3)	N/A†	Asymptomatic	21.0		X	X	X	X	X		21 / 352	20.5 (N/A)
17	Male	3	Microcephaly and others (29.2)	29.2	Asymptomatic	30.3	X	X			X			37 / 2042	28.0 (0.00)

*Percentile for head circumference for sex and age (intergrowth 21st)

†No microcephaly diagnosis